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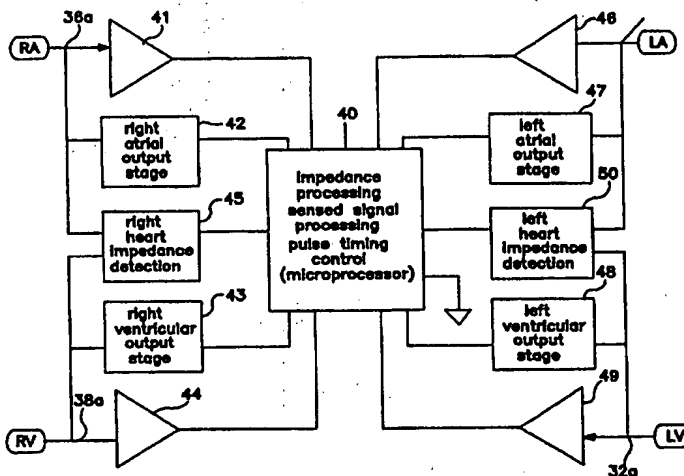
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(21) International Application Number: <b>PCT/US98/25915</b> (22) International Filing Date: <b>7 December 1998 (07.12.98)</b> (30) Priority Data: 08/990,427      15 December 1997 (15.12.97)      US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US      08/990,427 (CON) Filed on      15 December 1997 (15.12.97) (71) Applicant (for all designated States except US): <b>MEDTRONIC, INC. [US/US]; 7000 Central Avenue Northeast, Minneapolis, MN 55432 (US).</b> (72) Inventors; and (75) Inventors/Applicants (for US only): <b>BAKELS, Arnoldus [NL/NL]; Karolingenstraat 5, NL-6369 BV Simpelveld (NL). LEINDERS, Robert [NL/NL]; Maaslandstraat 9, NL-6141 BX Limbricht (NL). DE ROOS, Cubus [NL/NL]; Beneluxstraat 54, NL-6372 AZ Landgraaf (NL).</b> (74) Agents: <b>JARO, Michael, J. et al.; Medtronic, Inc. MS301, 7000 Central Avenue Northeast, Minneapolis, MN 55432 (US).</b>		(81) Designated States: <b>AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</b>  <b>Published</b> <i>With international search report.</i>

(54) Title: **FOUR-CHAMBER PACING SYSTEM FOR OPTIMIZING CARDIAC OUTPUT**

## (57) Abstract

A pacing system and method for providing multiple chamber pacing of a patient's heart, and in particular, pacing programmed for treatment of various forms of heart failure. The system utilizes impedance sensing for determining optimum pacing parameters, e.g., for pacing the left ventricle so that left heart output is maximized. The impedance sensing is also used for determination of arrhythmias or progression of heart failure. Impedance sensing is provided for between selected pairs of the four chambers, to enable optimizing of information for control and diagnosis. In a preferred embodiment of the invention, impedance measurements are obtained for determining the timing of right heart valve closure or right ventricular contractions, and the timing of delivery of left ventricular pace pulses is adjusted so as to optimally synchronize left ventricular pacing with the right ventricular contractions. Impedance sensing in the left heart also provides timing of mechanical contraction, and the pacemaker controls pacing to maintain bi-ventricular mechanical synchronization adjusted for maximum cardiac output.

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## FOUR-CHAMBER PACING SYSTEM FOR OPTIMIZING CARDIAC OUTPUT

FIELD OF THE INVENTION

5 This invention relates to cardiac pacing systems and, more particularly, to four-chamber pacing systems with sensors for measuring cardiac mechanical characteristics so as to improve cardiac output for congestive heart failure and other patients.

BACKGROUND OF THE INVENTION

10 Congestive heart failure (CHF) is defined generally as the inability of the heart to deliver enough blood to the peripheral tissues to meet metabolic demands. Frequently CHF is manifested by left heart dysfunction, but it can have a variety of sources. For example, CHF patients may have any one of several different conduction defects. The natural electrical activation system through the heart involves sequential  
15 events starting with the sino-atrial (SA) node, and continuing through the atrial conduction pathways of Bachmann's bundle and internodal tracts at the atrial level, followed by the atrio-ventricular (AV) node, Common Bundle of His, right and left bundle branches, and final distribution to the distal myocardial terminals via the Purkinje fiber network. A common type of intra-atrial conduction defect is known as  
20 intra-atrial block (IAB), a condition where the atrial activation is delayed in getting from the right atrium to the left atrium. In left bundle branch block (LBBB) and right bundle branch block (RBBB), the activation signals are not conducted in a normal fashion along the right or left bundle branches respectively. Thus, in a patient with bundle branch block, the activation of the ventricle is slowed, and the QRS is seen to  
25 widen due to the increased time for the activation to traverse the conduction path.

CHF manifested by such conduction defects and/or other cardiomyopathies are the object of considerable research into treatments for improving cardiac output. For example, drug companies have recognized CHF as a market opportunity, and are conducting extensive clinical studies organized to test the  
30 outcome of newly developed drugs in terms of improving cardiac performance in

these patients. Likewise, it is known generally that four-chamber cardiac pacing is feasible, and can provide significant improvement for patients having left atrial-ventricular dysfunction, or other forms of cardiac heart failure. While there has been relatively little commercialization of four-chamber pacing, the hypothesis remains that cardiac pump function can clearly be improved by such pacing.

The benefits of four-chamber pacing generally have been disclosed and published in the literature. Cazeau et al., *PACE*, Vol. 17, November 1994, Part II, pp. 1974-1979, disclose investigations leading to the conclusion that four-chamber pacing is feasible, and that in patients with evidence of interventricular dyssynchrony, a better mechanical activation process can be obtained by resynchronizing depolarization of the right and left ventricles, and optimizing the AV sequence on both sides of the heart. In the patent literature, U.S. Patent No. 4,928,688 is representative of a system for simultaneous left ventricular (LV) and right ventricular (RV) pacing; natural ventricular depolarizations are sensed in both chambers, if one chamber contracts but the other one does not within a window of up to 5-10 ms, then the non-contracting ventricular chamber is paced.

In addition to the above-mentioned disclosures concerning the advantages of substantially simultaneous or synchronous pacing of the two ventricles, it is known that there is an advantage to synchronous pacing of the left atrium and the right atrium for patients with IAB, inter-atrial block. In a normal heart, atrial activation initiates with the SA node, located in the right atrial wall. In a patient with IAB, the activation is slow being transferred over to the left atrium, and as a result the left atrium may be triggered to contract up to 90 ms later than the right atrium. It can be seen that if contractions in the left ventricle and the right ventricle are about the same time, then left AV synchrony is way off, with the left ventricle not having adequate time to fill up. The advantage of synchronous pacing of the two atria for patients with IAB is disclosed at *AHA* 1991, Abstract from 64th Scientific Sessions, "Simultaneous Dual Atrium Pacing in High Degree Inter-Atrial Blocks: Hemodynamic Results," Daubert et al., No. 1804. Further, it is known that patients with IAB are susceptible to retrograde activation of the left atrium, with resulting

atrial tachycardia. Atrial resynchronization through pacing of the atria can be effective in treating the situation. *PACE*, Vol. 14, April 1991, Part II, p. 648, "Prevention of Atrial Tachyarrhythmias Related to Inter-Atrial Block By Permanent Atrial Resynchronization," Mabo et al., No. 122. For patients with this condition, a criterion for pacing is to deliver a left atrial stimulus before the natural depolarization arrives in the left atrium.

In view of the published literature, it is observed that in CHF patients improved pump function can be achieved by increasing the filling time of the left ventricle, i.e., improving the left AV delay, and specifically the left heart mechanical AV delay (MAVD); decreasing mitral valve regurgitation, (back flow of blood through the nearly closed valve) by triggering contraction of the left ventricle when and as it becomes filled; and normalizing the left ventricular activation pattern, i.e., the time sequence of left atrial contraction relative to right atrial contraction. More specifically, for a cardiac pacing system used for treating a CHF patient, the aim is to capture the left atrium; optimize the left AV delay so as to properly fill the left ventricle and provide a more normal AV delay; and activate the left ventricle as much as possible in accordance with the natural propagation path of a healthy left heart. Particularly, left ventricular timing with respect to the left atrial contraction is crucial for improving cardiac output. The mechanical closure point of the left, or mitral valve, is a crucial moment which needs to be adjusted by programming of the left AV delay. Correct programming of this variable is key for optimizing the filling of the left ventricle, and optimizing ejection fraction, or cardiac output (CO).

An observation which is important to this invention is that the exact timing of mechanical events are important for properly controlling pacing so as to optimize left ventricular output. Specifically, it is known that actual contraction of one ventricular chamber before the other has the effect of moving the septum so as to impair full contraction in the later activated chamber. Thus, while concurrent or simultaneous pacing of the left and right ventricle may achieve a significant improvement for CHF patients, it is an aim of this invention to provide for pacing of the two ventricles in such a manner that the actual mechanical contraction of the left

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ventricle, with the consequent closing of the valve, occurs in a desired time relationship with respect to the mechanical contraction of the right ventricle and closing of the right valve. For example, if conduction paths in the left ventricle are impaired, delivering a pacing stimulus to the left ventricle at precisely the same time as to the right ventricle may nonetheless result in left ventricular contraction being slightly delayed with respect to the right ventricular contraction. As a consequence, it is important for this invention to provide a technique for measurement of mechanical events, such as a mechanical closure point of each of the ventricles, so as to be able to accurately program the sequence of pacing to achieve the desired dual ventricular pacing which optimizes ejection fraction, or cardiac output, for the individual patient.

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In view of the above-noted importance of measuring mechanical events, such as mitral or tricuspid valve closure, and the importance of measuring cardiac output, it is necessary for the pacing system of this invention to employ sensors which can provide this information. It is known to use impedance sensors in pacing systems, for obtaining information concerning cardiac function. For example, reference is made to U.S. Patent No. 5,501,702, incorporated herein by reference, which discloses making impedance measurements from different electrode combinations. In such system, a plurality of pace/sense electrodes are disposed at respective locations, and different impedance measurements are made on a time/multiplexing basis. As set forth in the referenced patent, the measurement of the impedance present between two or more sensing locations is referred to "rheography." A rheographic, or impedance measurement involves delivering a constant current pulse between two "source" electrodes, such that the current is conducted through some region of the patient's tissue, and then measuring the voltage differential between two "recording" electrodes to determine the impedance therebetween, the voltage differential arising from the conduction of the current pulse through the tissue or fluid between the two recording electrodes. The referenced patent discloses using rheography for measuring changes in the patient's thoracic cavity; respiration rate; pre-ejection interval; stroke volume; and heart tissue contractility. It is also known to use this technique of four point impedance measurements, applied thoracically, for



measuring small impedance changes during the cardiac cycle, and extracting the first time derivative of the impedance change,  $dZ/dt$ . It has been found that a substantially linear relation exists between peak  $dZ/dt$  and peak cardiac ejection rate, providing the basis for obtaining a measure of cardiac output. See also U.S. Patent No. 4,303,075, disclosing a system for measuring impedance between a pair of electrodes connected to or in proximity with the heart, and processing the variations of sensed impedance to develop a measure of stroke volume. The AV delay is then adjusted in an effort to maximize the stroke volume.

Given the demonstrated feasibility of four-chamber cardiac pacing, and the availability of techniques for sensing natural cardiac signals and mechanical events, there nonetheless remains a need for developing a system which is adapted to the cardiac condition of a patient with CHF, so as to provide pacing sequences which are tuned for improving cardiac output, and in particular for improving left heart function. It is a premise of this invention that such a system is founded upon accurate measurements of mechanical events, and use of the timing of such mechanical events to control and program pacing sequences.

#### SUMMARY OF THE INVENTION

It is an overall object of this invention to provide a pacing system for multiple chamber pacing, and in particular, for pacing the patient's left heart in coordination with the electrical activation and mechanical events of the patient's right heart, so as to optimize left heart output. In accordance with this invention, there is provided a four-chamber pacing system, having leads carrying electrodes positioned for pacing and sensing in or on each of the four cardiac chambers. Additionally, the leads are connected to obtain impedance measurements from which accurate timing signals are obtained reflecting mechanical actions, e.g., valve closures, so that accurate timing information is available for controlling electrical activation and resultant mechanical responses for the respective different chambers. The impedance or mechanical sensing determinations are preferably made by multi-plexing through fast switching networks to obtain the desired impedance measurements in different chambers.

In a preferred embodiment, control of four-chamber pacing, and in particular left heart pacing, is based primarily upon initial detection of a spontaneous signal in the right atrium, and upon sensing of mechanical contraction of the right and left ventricles. In a heart with normal right heart function, the right mechanical AV delay is monitored to provide the timing between the initial sensing of right atrial activation (P-wave) and right ventricular mechanical contraction. The left heart is controlled to provide pacing which results in left ventricular mechanical contraction in a desired time relation to the right mechanical contraction; e.g., either simultaneous or just preceding the right mechanical contraction; cardiac output is monitored through impedance measurements, and left ventricular pacing is timed to maximize cardiac output. In patients with intra-atrial block, the left atrium is paced in advance of spontaneous depolarization, and the left AV delay is adjusted so that the mechanical contractions of the left ventricle are timed for optimized cardiac output from the left ventricle.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic representation of a system in accordance with this invention, whereby four bipolar leads are provided, the leads being shown carrying bipolar electrodes positioned in each of the respective cardiac chambers.

Fig. 2A is a block diagram of a four channel pacing system in accordance with this invention, for pacing and sensing in each ventricle, and for obtaining impedance signals from the left heart and the right heart; Fig. 2B is a schematic representation of an arrangement in accordance with this invention for detecting left ventricular impedance for determination of cardiac output.

Fig. 3 is a block diagram of a four-chamber pacemaker with the ability to time multiplex impedance measurements, in accordance with this invention.

Fig. 4 is a block diagram of a system implementation in accordance with an embodiment of this invention for controlling left ventricular pacing in a patient with LBBB.

Fig. 5 is a flow diagram for a system implementation in accordance with an embodiment of this invention, for controlling left atrial and ventricular pacing in a patient with IAB.

Fig. 6 is a flow diagram of a routine in accordance with this invention for optimizing bi-ventricular pacing to provide maximum cardiac output.

Fig. 7 is a block schematic of a pacemaker in accordance with this invention for providing selectable four-chamber pacing and cardiac signal sensing, as well as impedance sensing between selected combinations of the four heart chambers.

Fig. 8A is a flow diagram of a process using inter-atrial or inter-ventricular impedance measurements for determination of existence of arrhythmias; Fig. 8B is a flow diagram illustrating a procedure for obtaining atrio-ventricular cross-impedance measurements for obtaining indications of heart failure.

#### DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the description of the preferred embodiments, and with reference to the drawings, the following designations are used:

DRAWING DESIGNATION	DEFINITION
RA	right atrium
RV	right ventricle
RH	RA and RV
LH	LA and LV
LA	left atrium
LV	left ventricle
LAS	left atrial sense
RAS	right atrial sense
LAP	left atrial pace pulse
LVP	left ventricular pace pulse
RMAVD	time interval between RAS and mechanical contraction of RV (as measured, e.g., by valve

	closure)
LMAVD	time interval between LAS or LAP and mechanical contraction of LV
RAVD	time interval between RAS and QRS in RV
LAVD	time interval between LAS or LAP, and QRS in LV

Referring now to Fig. 1, there is shown a schematic representation of a four-chamber pacing system, illustrating four pacing leads providing bipolar electrodes positioned for pacing and sensing in each of the respective heart chambers, and also for impedance measurements. Pacing lead 38 is positioned conventionally such that its distal end is in the right ventricular apex position. It carries bipolar electrodes 38a and 38b adapted for pacing and sensing; additionally, these electrodes can also be used for impedance sensing as discussed below. Likewise, atrial lead 36 is positioned so that its distal end is positioned within the right atrium, with bipolar electrodes 36a, 36b. Lead 34 is passed through the right atrium, so that its distal end is positioned in the coronary sinus for pacing, sensing and impedance detection through electrodes 34a, b, as shown. Likewise, lead 32 is positioned via the coronary sinus a cardiac vein, e.g., the middle or great cardiac vein, so that distal electrodes 32a and 32b are positioned approximately as shown for pacing, sensing and impedance detection with respect to the left ventricle. The pacing leads are connected to pacemaker 30 in a conventional manner. It is to be understood that each of the four leads can have one or more additional electrodes; however, by using time multiplexing techniques as discussed below and in the referenced U.S. Patent No. 5,501,702, pacing, sensing and impedance detection can be accomplished with only two electrodes per lead. Referring now to Figs. 2A and 2B, there is shown a simplified block diagram of a four channel pacemaker in accordance with this invention, having the additional capability of impedance detection to sense valve movement of the left and right ventricles. Although discussion of Fig. 2A is

presented with respect to valve movement, it is to be understood that the impedance detection scheme may be altered to detect other mechanical events, such as ventricular wall contraction, in a known manner.

5 The system of Fig. 2A contains, in the pacemaker, a central processing block 40, indicated as including timing circuitry and a microprocessor, for carrying out logical steps in analyzing received signals, determining when pace pulses should be initiated, etc., in a well known fashion. Referring to the upper left-hand corner of the block diagram, there is shown signal amplifier circuitry 41, for receiving a signal from the right atrium. Electrode 36a is illustrated as providing an input, it being understood that the second input is received either from bipolar electrode 36b, or via an indifferent electrode (the pacemaker can) in the event of unipolar sensing. 10 Likewise, a pulse generator 42, acting under control of block 40, generates right atrial pace pulses for delivery to electrode 36a and either electrode 36b or system ground. In a similar manner, right ventricular pace pulses (RVP) are generated at output stage 43 and connected to electrode 38a, and sensed right ventricular signals are inputted to sense circuitry 44, the output of which is delivered to control block 40. Also 15 illustrated is impedance detector 45, which receives inputs from electrodes 36a, 38a, for delivering information corresponding to right heart valve closure, which timing information is inputted into control block 40. Thus, the system enables pacing and sensing in each chamber, as well as impedance detection to provide an indication of the timing of right heart valve closure, which represents the time of mechanical contraction of the right valve.

Still referring to Fig. 2A, there are shown complementary circuit components for the left atrium and the left ventricle. Output generator stage 47, under control of block 40, delivers left atrial pace pulses (LAP) to stimulate the left atrium through electrode 34a and either electrode 34b or system ground. Inputs from the left atrial lead are connected through input circuitry 46, the output of which is connected through to control block 40. In a similar fashion, output stage 48, under control of block 40, provides left ventricular stimulus pace pulses (LVP) which are delivered across electrode 32a and either electrode 32b or system ground; and left ventricular 25 30

signals are sensed from lead 32 and inputted to input circuit 49, which provides an output to block 40 indicative of left ventricular signals. Also, dual inputs from the left atrial electrode 34a and left ventricular electrode 32a are inputted into left heart impedance detector 50, which provides timing pulses to block 40 indicative of the timing of left heart (mitral) valve closure. With this arrangement, the pacemaker has the basic timing and cardiac signal information required to program delivery of pace pulses to respective heart chambers in accordance with this invention. Block 40 contains current generators for use in impedance detection; microprocessor or other logic and timing circuitry; and suitable memory for storing data and control routines.

Referring to Fig. 2B, there is shown a diagrammatic sketch of an arrangement for detecting left ventricular impedance change, which is processed in block 40 to obtain an indication of cardiac output. As shown, a current source 52 provides a constant current source across electrode 53 in the right atrium, which suitably can be electrode 36a; and right ventricular electrode 54, which suitably can be electrode 38a. The current source can be pulsed, or it can be multiplexed in a manner as discussed below. Impedance sensors 57 and 58 provide signals representative of impedance changes therebetween, the impedance being a function of blood volume and valve closure, as discussed above. The outputs from electrodes 57, 58 is connected across impedance detector 56, which represents the microprocessor and/or other processing circuitry in block 40 for analyzing the impedance changes and making a determination of cardiac output. As is known, a measure of cardiac output can be obtained by extracting the first time derivative of cyclical impedance changes,  $dz/dt$ ; a linear relationship exists between peak  $dz/dt$  and peak ejection rate.

Referring now to Fig. 3, there is shown a block diagram of a pacemaker 30 in accordance with a preferred embodiment of this invention, for multiplexing connections to electrodes so as to provide for pacing and sensing in any one of the four cardiac chambers, as well as for impedance determinations between respective different lead electrodes. Reference is made U.S. Patent No. 5,501,702, incorporated herein by reference, for a full discussion of this circuit, and in particular the multiplexing arrangement carried out by switch matrices 68, 70. The pacemaker

30 operates under control of circuitry 62, which may include a microprocessor or custom integrated circuitry, as well as associated memory, in a manner well known in the pacemaker art. Circuitry 62 provides for processing of data, and generation of timing signals as required. Control circuitry 62 is coupled to pace/sense circuitry 64, for processing of signals indicating the detection of electrical cardiac events, e.g., P-waves, R-waves, etc. sensed from conductors which connect electrically to electrodes 32a-38b, as shown. The aforementioned leads are also coupled to a first switch matrix 68 and a second switch matrix 70. Matrix 68 establishes a selectable interconnection between specific ones of the electrodes of leads 32, 34, 36 and 38, and the current source 72, is controlled by circuit 62. In a similar manner, switch matrix 70 establishes a selectable interconnection between lead conductors corresponding to selected electrodes, and impedance detection circuit 74, for the purpose of selecting impedance measurements.

Still referring to Figure 3, current source 72 receives control signals on line 73 from circuitry 62, and is responsive thereto for delivering constant current rheography pulses onto lead conductors selected by switching matrix 68, which in turn is switched by signals on bus 83. Impedance detection circuit 74 is adapted to monitor the voltage between a selected pair of electrodes which pair is selectably coupled by operation of switch matrix 70 which in turn is switched by signals on bus 80. In this manner, circuit 74 determines the voltage, and hence the impedance, existing between two selected electrodes. The output of circuitry 74 is connected through A/D converter 76 to control circuitry 62, for processing of the impedance signals and determination of the occurrence of mechanical events, such as left or right heart valve closure. The control of switch matrix 68 through signals on bus 78, and the control of switch matrix 70 through signals on bus 80, provides for multiplexing of different impedance signals.

It is to be understood that in the system arrangement of Figure 3, pace/sense circuitry 64 may include separate stimulus pulse output stages for each channel, i.e., each of the four-chambers, each of which output stages is particularly adapted for generating signals of the programmed signal strength. Likewise, the sense

circuitry of block 64 may contain a separate sense amplifier and processor circuitry for sensed signals from each chamber, such that sensing of respective wave portions, such as the P-wave, R-wave, T-wave, etc. from the RH and the LH, can be optimized. The pulse generator circuits and sense circuits as used herein are well known in the pacemaker art. In addition, other functions may be carried out by the control circuitry including standard pacemaker functions such as compiling of diagnostic data, mode switching, etc.

Referring now to Fig. 4, there is shown a logic control flow diagram for controlling the system of this invention to pace a patient with LBBB. The assumption is that the RH is normal, and that sinus signals from the SA node are being normally conducted to the LA; but that the LBBB is manifested by slow conduction to the LV, such that the LV does not contract when it should. As a consequence, there is mitral regurgitation, or backflow of blood through the valve because the LV does not contract when it is filled from the LA; and the contraction of the LV, when it occurs, is later than that of the RV, further contributing to decrease of LH output.

As seen at 101, the pacemaker monitors the RH, and gets a measure of RMAV. This is done by sensing right valve closure through RH impedance measurement, and timing the delay from the atrial depolarization (RAS) to valve closure. Then, at 102, the pacemaker is controlled to pace LV with an LAVD such that LMAVD is about equal to RMAVD. During this step, impedance measurements are made in the LV, and a measure of LMAVD is obtained. Based on this determination, the value of LAVD is adjusted to substantially match LMAVD with RMAVD. Note that normal conduction through the LV takes on the order of 50-60 ms, so it is expected that the LV should be paced in advance of the occurrence of RV valve closure, so that LV valve closure occurs at about the same time as, or even a bit before RV valve closure. Causing the LV to contract just before the RV might provide an increase of LH output which outweighs the small resulting RV dysfunction due to the septum being pulled toward the LV first. Thus, the timing of delivery of each LVP is adjusted to set LMAVD approximately equal to RMAVD. Then, at 104,



the value of LAVD is further adjusted, while R and L valve closure is monitored, and LMAVD is adjusted relative to RMAVD. This adjustment, or variation of LMAVD, may be made by incrementally changing LAVD each cycle, or each n cycles, to scan relative to the value of RMAVD. Cardiac output is obtained through a left heart impedance measurement, and appropriate signal processing, for each setting of the differential between the right and left valve closures, and respective values of CO and LMAVD are stored at 105. The highest, or maximum value of cardiac output is determined, and LAVD is set so that the resultant MLAVD is at the differential compared to RMAVD to yield the highest cardiac output. In this manner, the timing of left ventricular pace pulses is set to produce substantial bi-ventricular mechanical synchronization for the greatest cardiac output. The determined value of LAVD and the corresponding LV-RV difference is stored.

Still referring to Fig. 4, at 106 the pacemaker proceeds to pace the LV with this established value of LAVD, providing mechanical synchronization. Of course, if the natural sinus rate varies, the pacemaker wants to follow; if the spontaneous RAVD varies, but the LAVD doesn't follow the change, the mechanical synchronization will be lost. Accordingly, at 107 the pacer monitors the natural sinus rate, or atrial pacing rate, and determines if there has been a significant change in atrial rate. If yes, at 109, the pacer adjusts LAVD accordingly to maintain mechanical sync for optimum output. Although not shown, the pacemaker can periodically go back to block 101 to re-determine the desired value of LAVD.

Referring now to Fig. 5, there is shown a flow diagram for pacing of a patient with IAB; such patient may have LBBB as well. Here, it is necessary to take control of the LA by pacing before atrial depolarization is conducted (late) to the LA. At 110, the pacemaker monitors the pattern of LA depolarization relative to RA depolarization, i.e., it determines the inter-atrial delay. At 111, it is determined whether the LA should be paced, based on the atrial depolarization pattern. If yes, the pacemaker sets an RA-LA delay at 112, which corresponds to a healthy heart, and which enables capture of the LA. At 114, the value of RMAVD is obtained, as was described in connection with Fig. 4. Then, at 116, LAVD is determined for a first

5 setting of mechanical sync; this can be done by setting LAVD to produce LV contraction at the same time as RV contraction (valve closure), or earlier by a small time increment. Then, LAVD is varied, as shown at 117, and LMAVD and CO are determined corresponding to each value of LAVD. The value of LAVD is set to that value which corresponds to maximum cardiac output, and this value and the LV-RV mechanical relation, or mechanical sync value is stored for the chosen LAVD. At 118, the pacemaker paces LA and LV, in accord with the values that have been determined. In the event of significant change in atrial rate, LAVD is adjusted to compensate for the rate change, and to substantially maintain the LV-RV mechanical relationship previously found to correspond to maximum cardiac output, as shown at 10 120, 121. Although not shown, in the event of large changes in the sinus rate, or passage of a predetermined amount of time, determination of inter-atrial delay and LAVD can be repeated automatically.

15 Referring now to Fig. 6, there is shown a simplified flow diagram for a procedure in accordance with this invention for carrying out bi-ventricular pacing so as to maximize cardiac output (CO). This routine is adapted for patients who need right ventricular pacing, and who can benefit from synchronous left ventricular pacing as well. In this example, it is assumed that atrial pacing is not required, but if the patient requires atrial pacing, the routine can be adapted appropriately.

20 At block 130, a common value of AV delay (AVD) is first set. At block 132, both the left ventricle and the right ventricle are paced, initially with the previously set value of AVD, but then with a varying AVD. As AVD is varied, or scanned relative to the initial setting, the pacemaker makes determinations of cardiac output by processing impedance signals from the left heart, or left ventricle, in the manner discussed above. Values of CO are stored together with the different values 25 of AVD, and the optimum value of a common AVD is determined corresponding to maximum CO. Then, at block 134, the value of LAVD is varied relative to RAVD, such that the left pacing pulse is delivered at differing times from the right pacing pulse. It is to be remembered, as discussed above, that for maximum cardiac output, it may be desirable to pace the left ventricle shortly before the right ventricle, and this 30

step is a searching step to determine the time relationship between the two ventricular pace pulses which results in the best cardiac output. CO is determined as the ventricular sync relationship is varied, and the corresponding optimum LAVD is determined. When this has been obtained, the routine goes to block 136 and paces the patient at the determined values of LAVD and RAVD. Periodically, as indicated at 138, the pacemaker can determine whether a test is desired. If yes, the routine branches back to 130, to loop through the test and redetermine the optimum values of LAVD and RAVD. It is to be noted that the steps of blocks 132 and 134 can be done in a reverse sequence, i.e., step 134 first and then step 132.

Referring now to Fig. 7, there is shown an alternate block diagram of component portions of a pacemaker in accordance with this invention, for providing maximum flexibility in terms of pacing, cardiac signal sensing and impedance sensing. At least two electrodes are positioned in or proximate to each heart chamber, in the manner as discussed above in connection with Fig. 1, and connected in turn to block 150. As indicated in Fig. 7, block 150 is an output/input switch matrix, and interconnects with block 152 in the manner as described in Fig. 3. Thus, block 152 provides pacing pulses which can be connected through matrix 150 to each of the four chambers, and has sense amplifier circuitry for sensing signals from each of the four chambers. Block 150 further provides a multiplex switch array for switching a current source across selected pairs of the eight electrodes for impedance measuring purposes, again in accordance with the discussion of Fig. 3. The sensed impedance signals are suitably transferred from array 150 to digital signal processing circuitry 161, which is part of block 152. Block 152 is in two-way connection with the timing modules shown in block 154, for timing generation of pace pulses, current source pulses, and the generation of sensing windows. Blocks 150, 152 and 154 are further interconnected by control bus 163. Data is transferred between signal processing block 170 and block 154 across data bus 157. Block 154 in turn is inter-connected with microprocessor 156, through household bus 151, data bus 153 and control bus 154. By this arrangement, impedance sensing can be carried out across any combination of the four heart chambers, e.g., right atrium vs. left atrium; right ventricle vs. left

ventricle; right atrium vs. left ventricle; and left atrium vs. right ventricle. Impedance measurements between these combinations of chambers can be carried out in accordance with this invention, for purposes of analyzing and confirming arrhythmias, including fibrillation. Further, changes in conduction patterns, as seen in the morphology of such impedance measurements, can be monitored and processed for making determinations of progression of heart failure. Thus, cross-measurements of RA-LV and LA-RV can be useful in obtaining histories to determine changes indicating progression of heart failure.

Referring now to Fig. 8A, at block 160, the pacemaker first obtains impedance measurements either between LA and RA, or between LV and RV. These impedance values are processed at 162, and at 164 a determination is made as to whether the atrial or ventricular rhythms are regular or non-physiological. This determination can be made, for example, simply by sensing differences over time and comparing such differences to predetermined criteria. If a rhythm is determined not to be regular, then a determination of arrhythmia is made at 166. A suitable response is made at 168. Referring to Fig. 8B, at block 170 the pacemaker obtains cross-measurements of impedances, e.g., between RA and LV or between LA and RV. These measurements are stored and processed as indicated at 172, and evaluated at 174 to determine whether they indicate HF or progression toward HF. If yes, an appropriate response can be made, illustrated at 176, e.g., providing a warning which can be retrieved by an external programmer.

The scope of the invention extends to other conditions of CHF, in addition to the ones illustrated here. In each case, the condition of the patient must be responded to on an individual basis. However, in accordance with this invention, the system response includes a determination of mechanical events, e.g., valve closure, preferably in each side of the heart, and programming of pacing escape intervals based on consideration of the mechanical events and a determination of variations of cardiac output with variations of LAVD and/or mechanical ventricular synchronization. The system of this invention can be used in an implanted pacemaker system; or, the system procedures can be carried out with an external system, for

determination of optimum programming of a pacemaker which is to be implanted or re-programmed.

**CLAIMS**

1. A pacing system for providing pacing of a patient's left heart, comprising:

first means for obtaining indications of mechanical contractions of the right ventricle;

left ventricular pacing means for pacing the left ventricle; and

LV control means for controlling the timing of said left ventricular pacing relative to indicated right ventricular mechanical contractions.

2. The pacing system as described in claim 1, comprising second means for obtaining indications of mechanical contractions of the left ventricle, and wherein said LV control means has means for controlling the timing of said left ventricular pacing so as to provide substantially synchronous left and right ventricular mechanical contractions.

3. The pacing system as described in claim 1, wherein said LV control means has means for delivering a left ventricular pacing pulse just before the expected time of the next right ventricular mechanical contraction.

4. The pacing system as described in claim 2, comprising left atrial pacing means for pacing the patient's left atrium; left AV control means for controlling the left AV delay between pacing the left atrium and the left ventricle, cardiac output means for measuring left heart output as a function of said left AV delay, and wherein said left AV control means further comprises maximizing means for adjusting said left AV delay to maximize left cardiac output.

5. The pacing system as described in claim 4, comprising means for sensing sinus signals, and left atrial timing means for timing delivery of left atrial pacing pulses relative to said sinus signals.

5           6.     The system as described in claim 1, wherein said first means comprises an impedance measuring circuit for obtaining an impedance signal representative of impedance between the patient's right atrium and right ventricle, and processing means for processing said impedance signal to determine the timing of right heart valve closures.

10           7.     The system as described in claim 1, comprising second impedance means for obtaining a left impedance signal representative of impedance change over the patient's left heart, and second processing means for processing said left impedance signal to obtain a measure of left heart output.

15           8.     The system as described in claim 7, comprising third processing means for processing said left impedance signal to obtain filling signals indicative of the filling of the left ventricle, and wherein said LV control means comprises means for controlling timing of said left ventricular pacing signals as a function of said filling signals.

20           9.     The system as described in claim 1, further comprising means for obtaining indications of left ventricular mechanical contractions, and wherein said LV control means comprises mechanical sync means for controlling said left ventricular pacing to achieve mechanical synchrony of said left and right mechanical contractions.

25           10.    The system as described in claim 9, wherein said mechanical sync means comprises adjusting means for adjusting the timing of aid left ventricular pacing so as to maximize left heart output.

          11.    A four-chamber pacing system for providing pacing of a patient's left heart to improve cardiac output, comprising:

RV means for determining the timing of right ventricular mechanical contractions;

LV means for determining the timing of left ventricular mechanical contractions; and

5           pacing sync means for pacing the patient's left ventricle; and

          control means for controlling said pacing means so as to substantially synchronize said left and right mechanical contractions;

10           12.   The four-chamber pacing system as described in claim 13, comprising:

          LA means for determining the timing of left atrial depolarization;

          CO means for measuring cardiac output from the patient's left heart; and

15           wherein said control sync means comprises LAVD means for controlling said pacing means to deliver pacing pulses to said patient's left ventricle at a left atrio-ventricular delay following left atrial depolarizations, and adjusting means for adjusting said left atrio-ventricular delay to correspond to maximum measured cardiac output.

20           13.   A system for bi-ventricular pacing, comprising:

          RVP generating means for generating and delivering pacing pulses to the patient's right ventricle;

25           LVP generating means for generating and delivering pacing pulses to the patient's left ventricle;

          atrial sense means for determining the cyclical time of excitation of the patient's right and left atria;

30           RAVD control means for controlling said RVP generating means to deliver pace pulses at a predetermined RAVD delay following right atrial activation;



LAVD control means for controlling said LVP generating means to generate pace pulses at an LAVD delay following left atrial activation;

output means for determining a measure of cardiac output from the patient's left ventricle;

5 adjusting means for adjusting said LAVD and RAVD delays and determining the optimum relationship of said LAVD and RAVD delays which results in maximized cardiac output; and

program means for programming said RAVD control means and said LAVD control means to control delivery of pacing pulses to the left and right  
10 ventricles with said optimum relation.

14. The system as described in claim 13, comprising second adjusting means for adjusting said LAVD and RAVD equally, and wherein said output means obtains values of LAVD and RAVD corresponding to maximum cardiac  
15 output and

wherein said program means controls said RAVD control means and said LAVD control means to deliver pacing pulses with said values.

15. The system as described in claim 14, comprising means for  
20 obtaining the difference between LMAVD and RMAVD corresponding to optimized cardiac output, and means for maintaining said difference.

16. A method of cardiac pacing, comprising:  
cyclically determining mechanical events indicative of left  
25 ventricular contraction and right ventricular contraction;  
cyclically determining cardiac output from the patient's left ventricle;

pacing said patient's left ventricle with varying timing relative to said right ventricular contractions and determining the relative mechanical

synchronization of left ventricular and right ventricular contractions which results in maximum cardiac output; and

maintaining said relative mechanical synchronization.

5                   17.    A method as described in claim 16, comprising:  
                      determining atrial excitations of the patient;  
                      controlling delivery of each left ventricular pace pulse at an  
LAVD delay following each said atrial excitation; and  
                      adjusting said LAVD to obtain said relative mechanical  
10                   synchronization for optimum cardiac output.

                  18.    The method as described in claim 16, comprising pacing the  
patient's right ventricle at an RAVD delay a following said atrial excitation, and  
controlling said RAVD and LAVD delays to maintain said relative mechanical  
15                   synchronization.

                  19.    The method as described in claim 17, comprising:

20                   20.    A method of bi-ventricular pacing, comprising sensing sinus  
signals from the patient's right atrium;  
                      cyclically generating and delivering left and right ventricular  
pace pulses for pacing the patient's left and right ventricles respectively;  
                      cyclically determining a measure of cardiac output from the  
patient's left ventricle; and  
25                   adjusting the relative timing of said left and right ventricular  
pace pulses to correspond to maximum cardiac output.

                  21.    The method as described in claim 20, comprising sensing  
patient-sinus signals, timing out an LAVD delay between a sensed sinus signal and  
30                   delivery of the left ventricular pace pulse and an RAVD delay between a sensed sinus

signal and delivery of a right ventricular pace pulse, varying said LAVD delay relative to said RAVD delay, and determining the relationship between said LAVD delay and said RAVD delay which results in said maximum cardiac output.

5                   22. The method as described in claim 21, having electrodes positioned in each of a patient's four heart chambers, comprising further adjusting both said LAVD and RAVD delays by equal amounts and determining the values of said delays corresponding to maximum cardiac output.

10                   23. A four chamber pacing system, having electrodes positioned in each of a patient's four heart chambers, comprising:

impedance means for obtaining impedance measurements between a selected pair of said four chambers;

15                   processing means for processing said impedance measurements, and determining changes in said measurements over a period of time; and

determining means for determining whether any said change occurs which indicates a physically abnormal heart condition.

20                   24. The system as described in claim 22, wherein said determining means determines whether any such change occurs which is indicative of an arrhythmia.

25                   25. The system as described in claim 22, wherein said determining means comprises means for determining whether said any such change occurs which indicates a heart failure condition.

30                   26. The system as described in claim 22, comprising programmable selection means for selecting impedance measurements between any two of said four heart chambers.

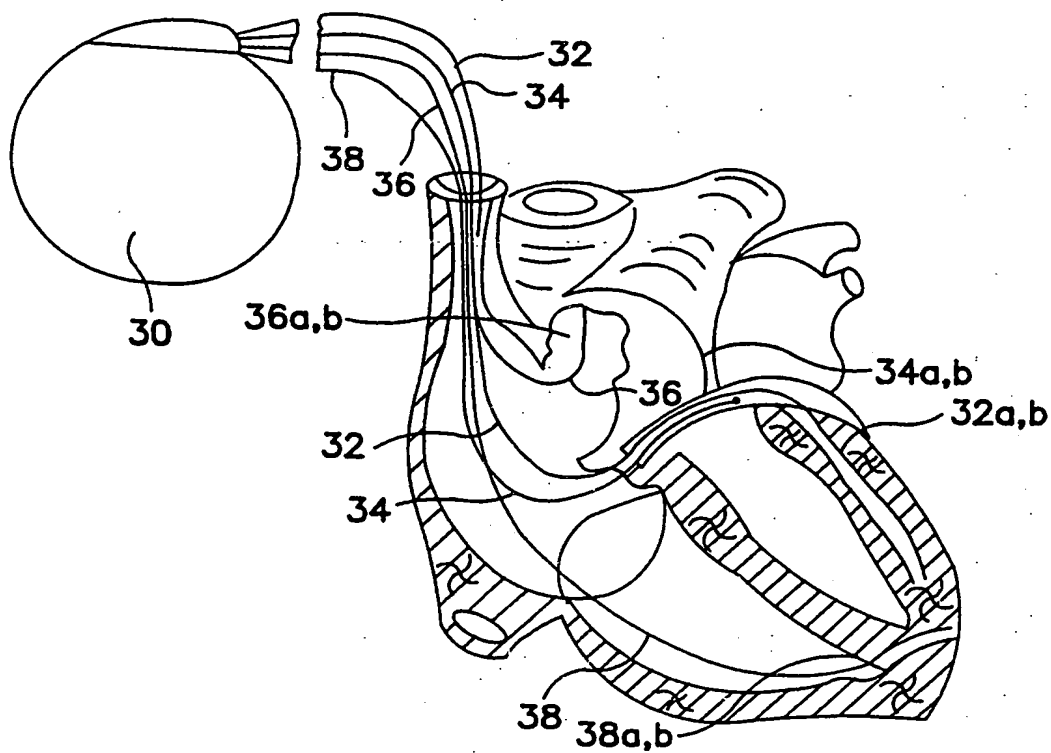


FIG. 1

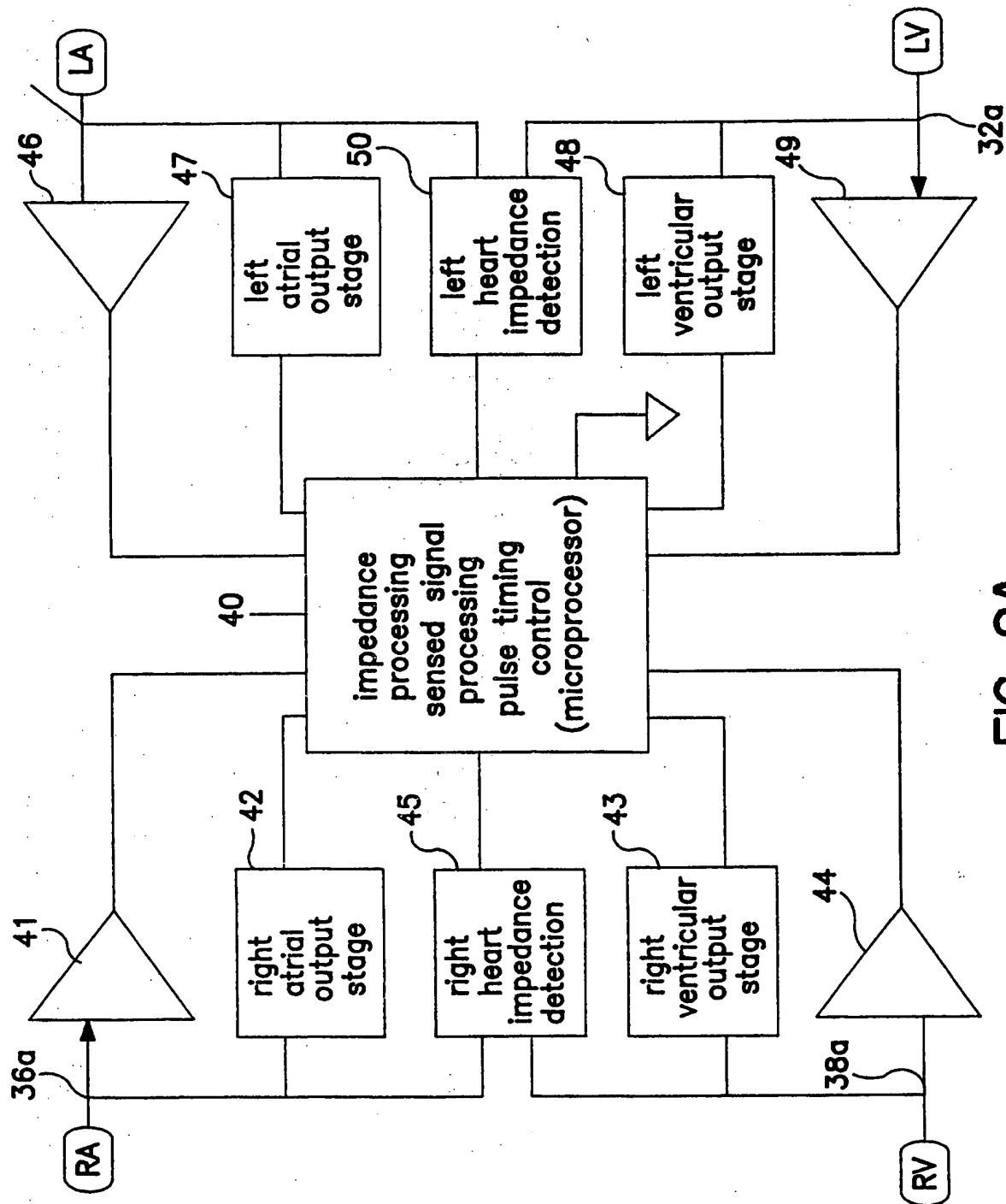


FIG. 2A

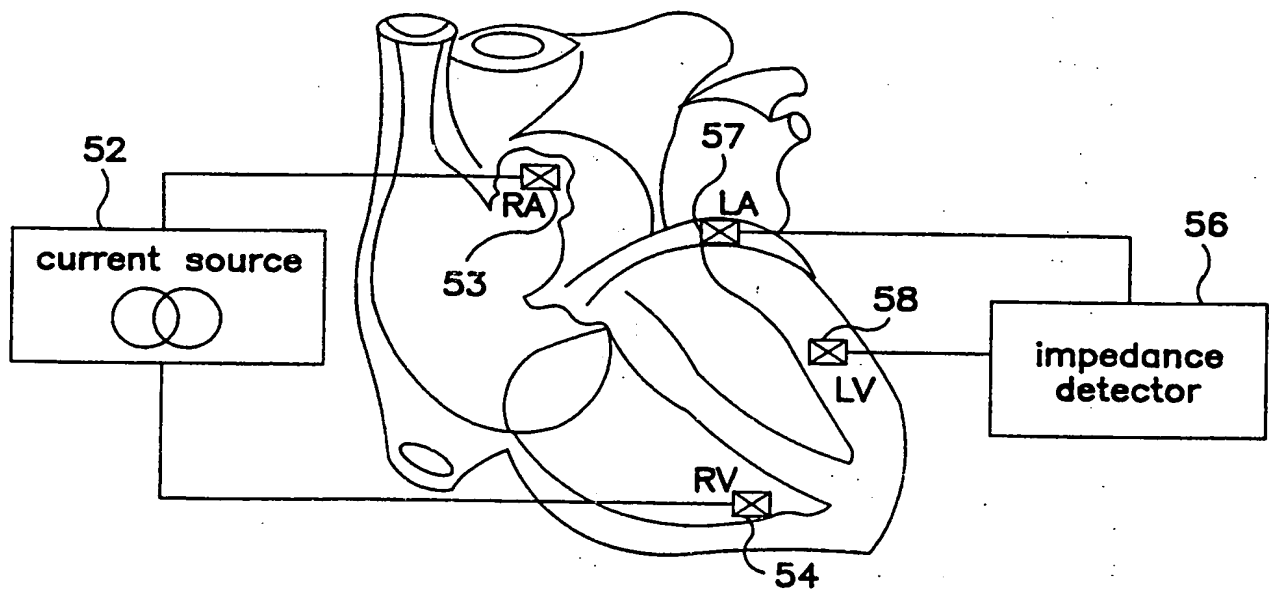


FIG. 2B

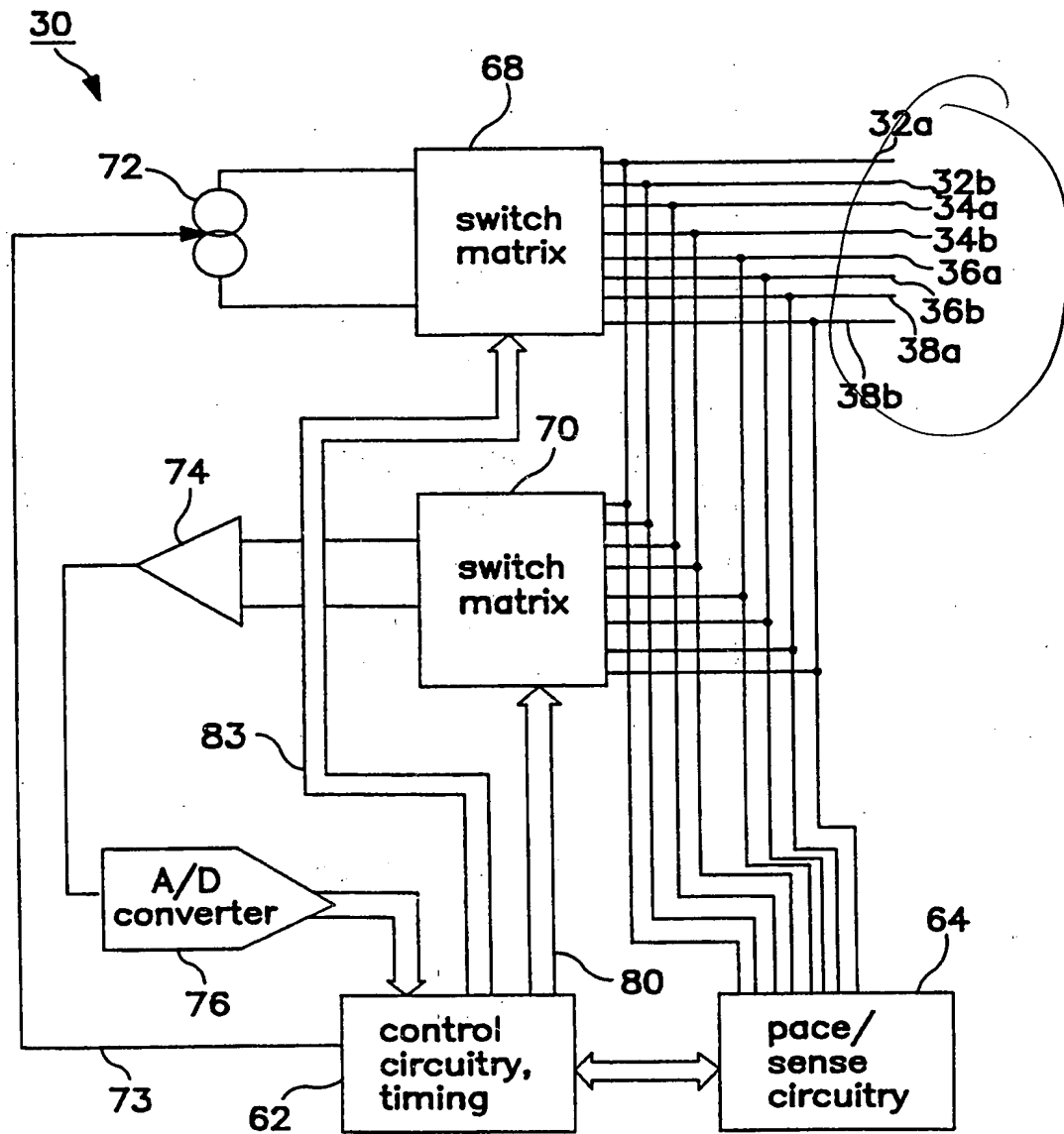


FIG. 3

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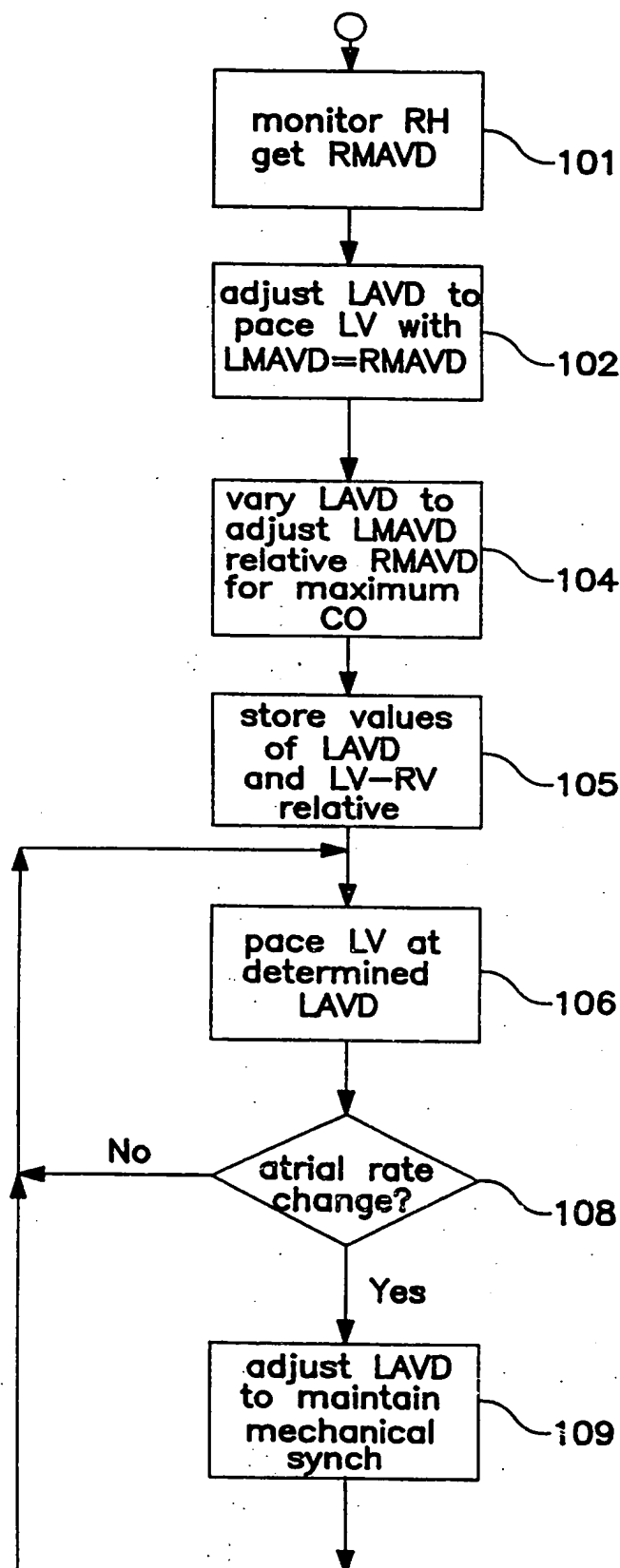


FIG. 4

SUBSTITUTE SHEET (RULE 26)



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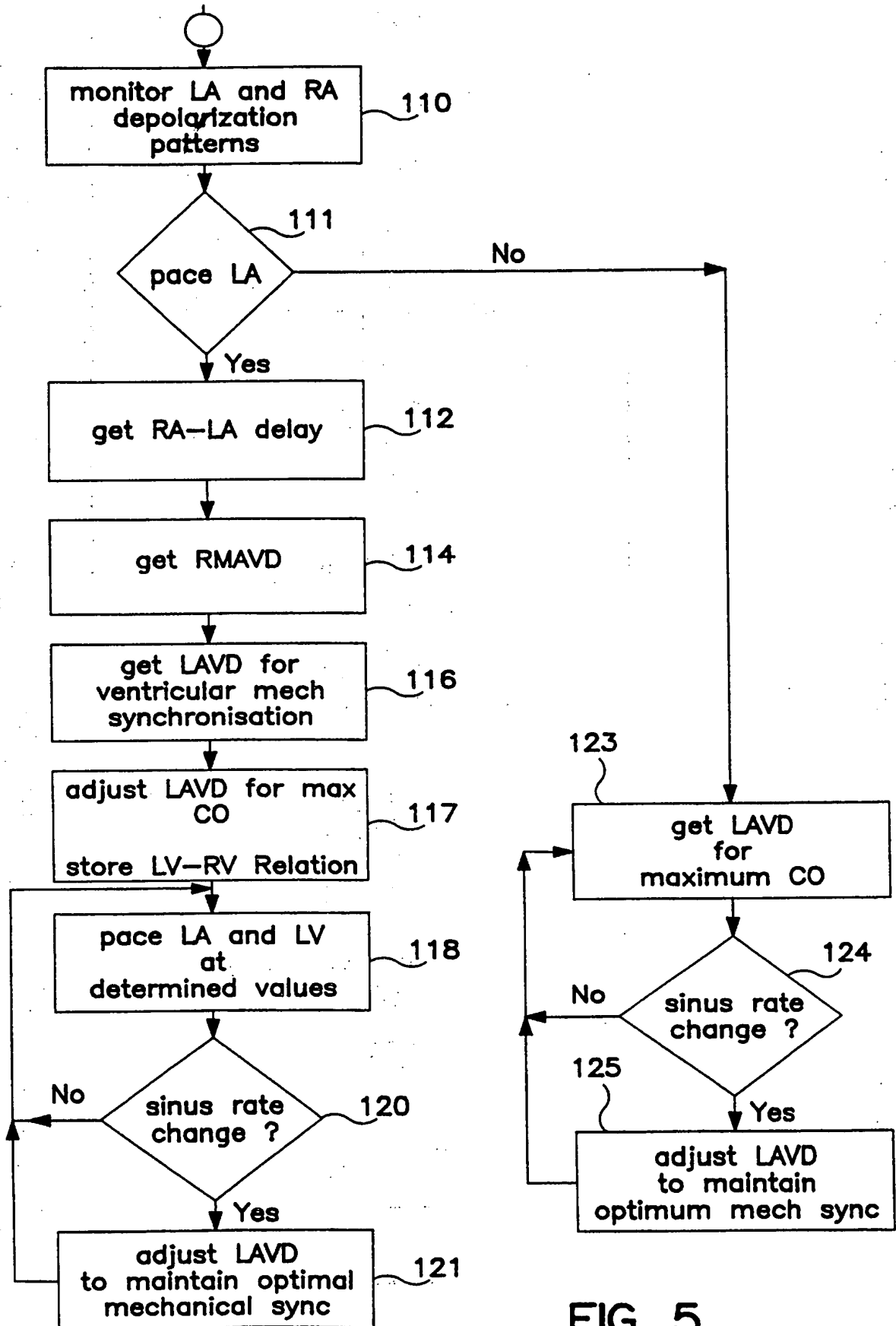


FIG. 5

SUBSTITUTE SHEET (RULE 26)

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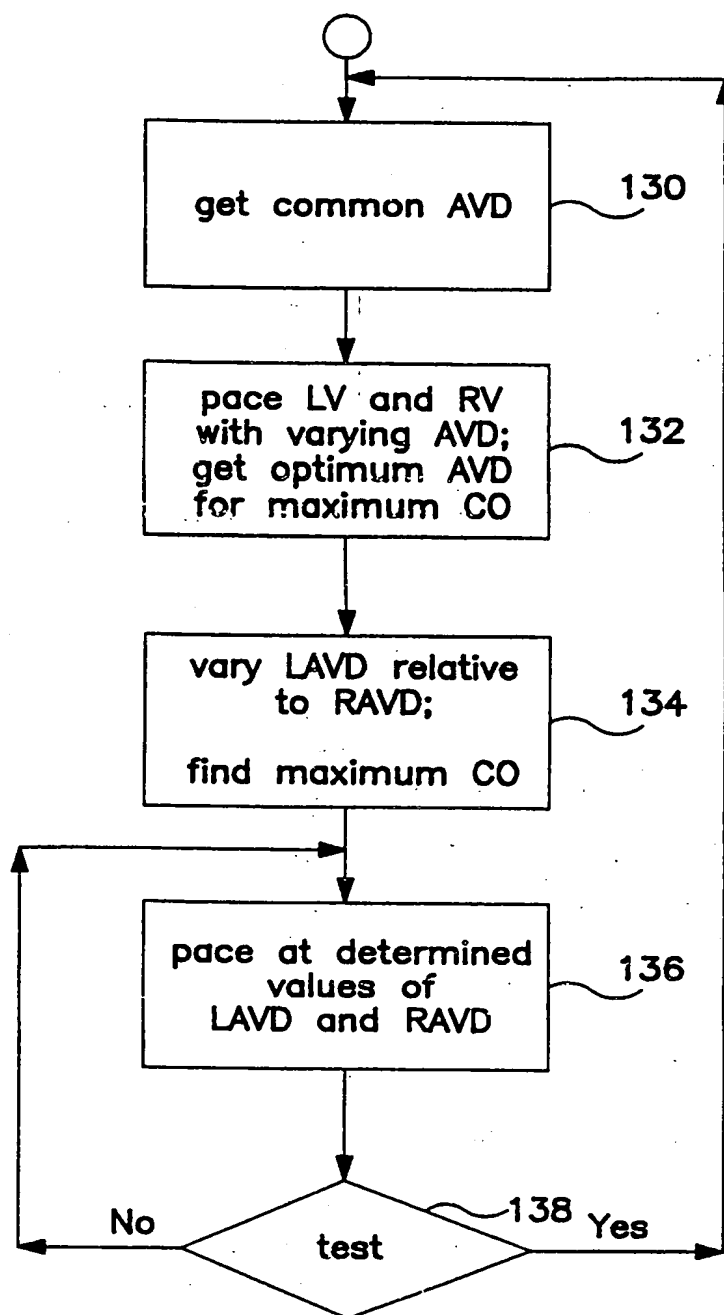
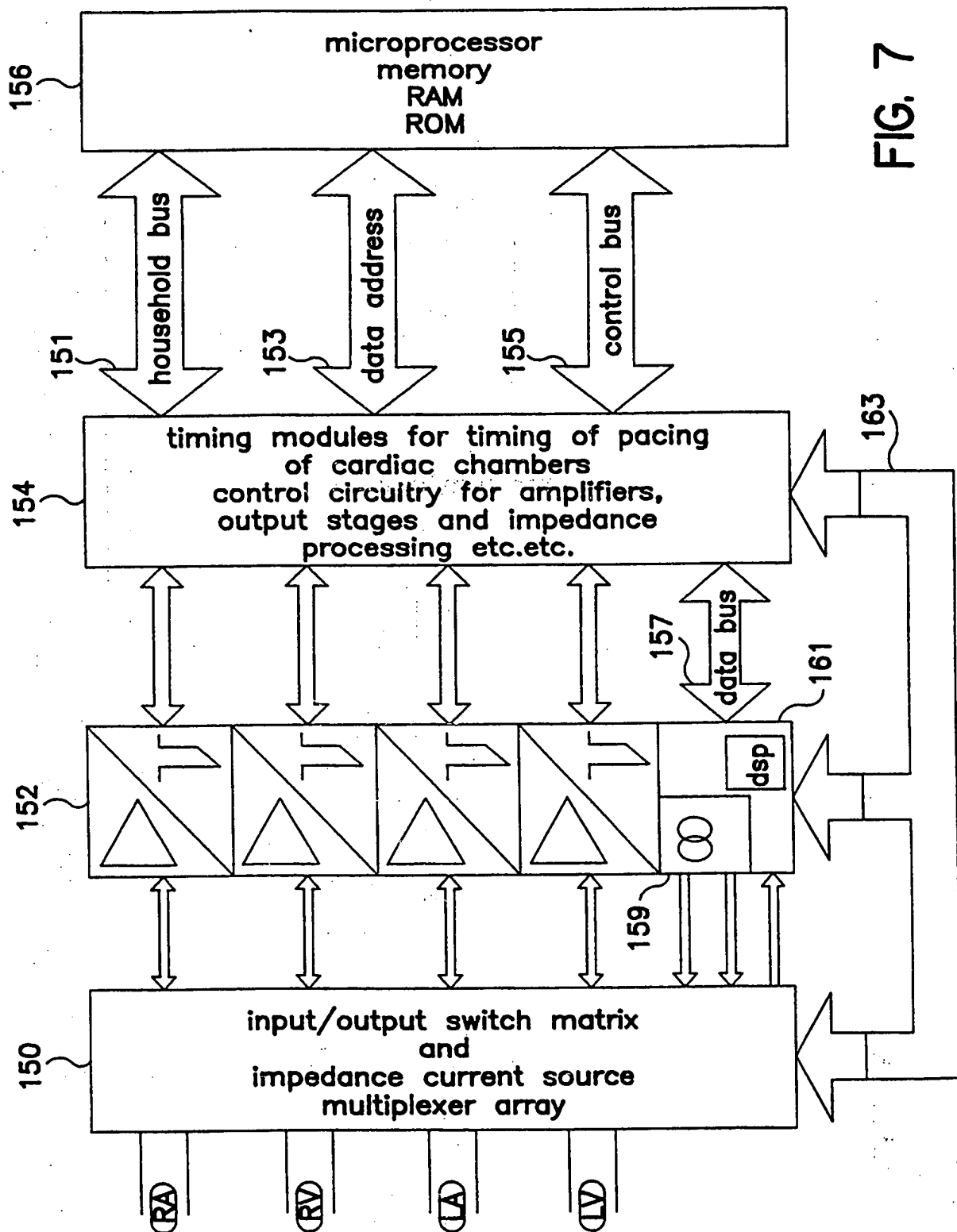


FIG. 6

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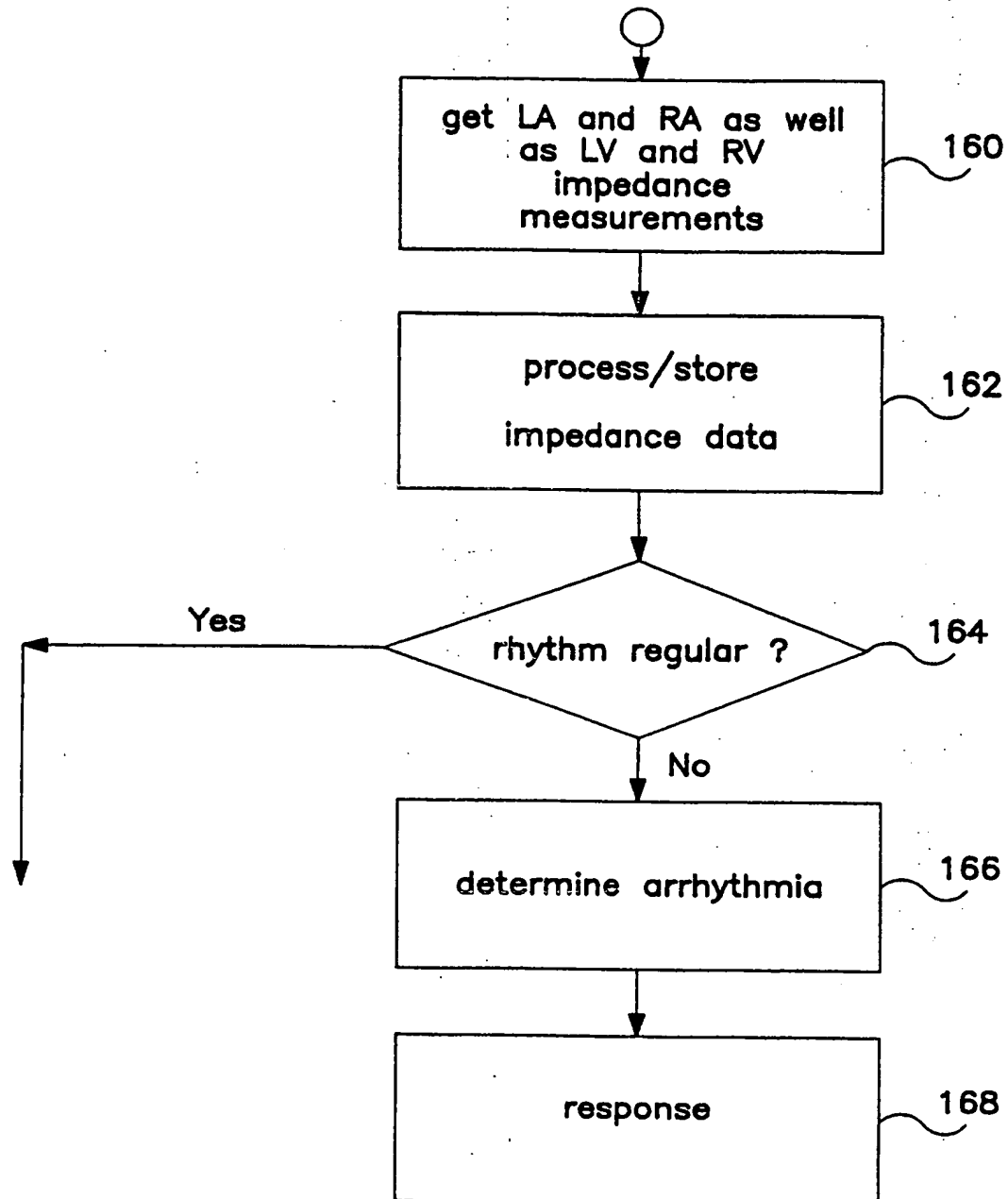


FIG. 8A

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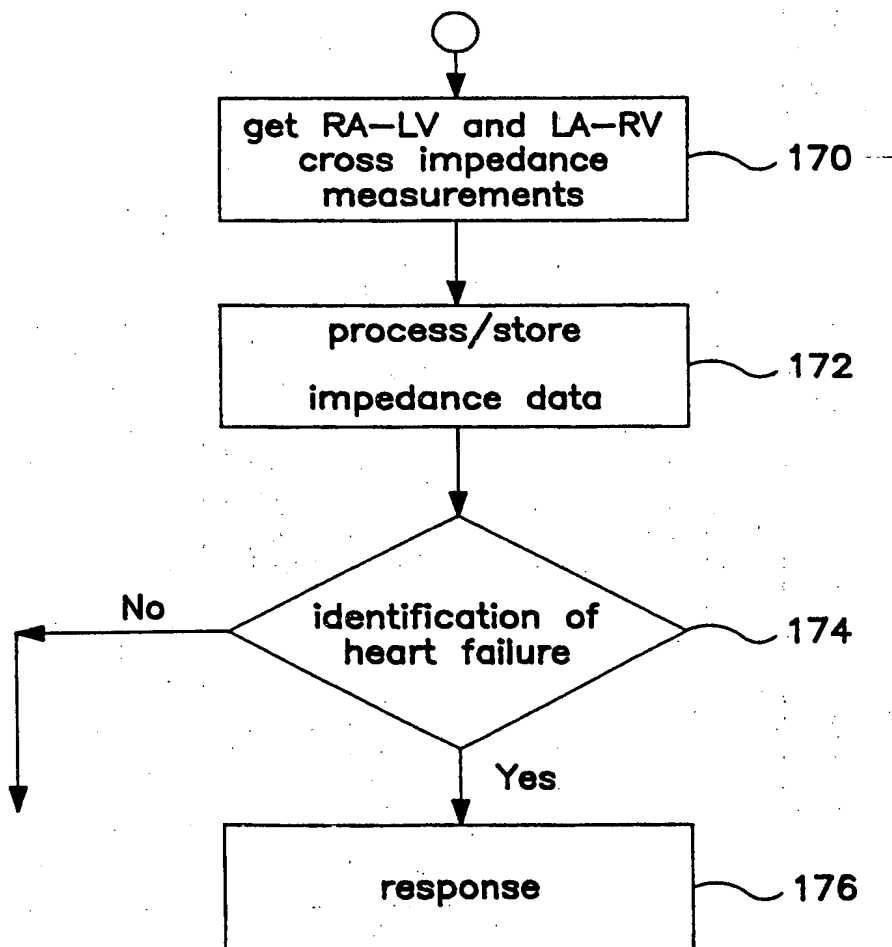


FIG. 8B

# INTERNATIONAL SEARCH REPORT

Int. l. Application No

PCT/US 98/25915

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61N1/368 A61N1/365

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 928 688 A (MOWER MORTON M) 29 May 1990 cited in the application	1, 2, 9
A	see column 5, line 16-49  see column 6, line 16-36	3, 11, 13, 23
A	CAZEAU S ET AL: "FOUR CHAMBER PACING IN DILATED CARDIOMYOPATHY" PACE, vol. 17, no. 11, November 1994, pages 1974-1979, XP000618630	1, 2, 5, 9, 11, 13, 23
A	US 5 540 727 A (SALO RODNEY W ET AL) 30 July 1996 see column 3, line 20-42 see column 4, line 24-30 see column 4, line 61 - column 5, line 7	1, 4, 5, 7, 9-13, 23
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

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"&" document member of the same patent family

Date of the actual completion of the international search

17 March 1999

Date of mailing of the international search report

24/03/1999

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/25915

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	OVSYSHCHER I E ET AL: "TOWARD PHYSIOLOGICAL PACING: OPTIMIZATION OF CARDIAC HEMODYNAMICS BY AV DELAY ADJUSTMENT" PACE - PACING AND CLINICAL ELECTROPHYSIOLOGY, vol. 20, no. 4, PART 01, April 1997, pages 861-865, XP000687688 cited in the application -----	4,6,7, 12,23
A	GB 2 070 282 A (MIROWSKI M) 3 September 1981 see page 2, line 33-70 -----	4,7,12, 23-25

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Information on patent family members

Int. l. Application No

PCT/US 98/25915

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